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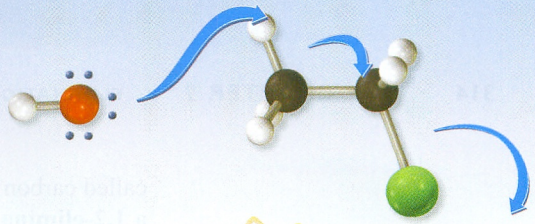


Elimination Reactions

REACTIONS OF ALKYL HALIDES, ALCOHOLS, AND RELATED COMPOUNDS

CHAPTER 9

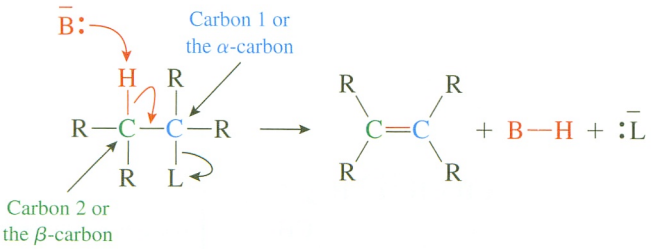
As we saw in Chapter 8, elimination reactions often compete with nucleophilic substitution reactions. Both reactions can be useful in synthesis if this competition can be controlled. This chapter discusses the two common mechanisms by which elimination reactions occur, the stereochemistry of the reactions, the direction of the elimination, and the factors that control the competition between elimination and substitution. Based on these factors, procedures are presented that can be used to minimize elimination if the substitution product is the desired one or to maximize elimination if the alkene is the desired product.

MASTERING ORGANIC CHEMISTRY

- Understanding the E2 Mechanism for Elimination, Including Its Stereochemistry and When It Is Favored
- Understanding the E1 Mechanism for Elimination, Including Its Stereochemistry and When It Is Favored
- Using Zaitsev's Rule and Hofmann's Rule to Predict Elimination Products
- Predicting the Products of Elimination Reactions
- Predicting the Major Reaction Pathway of Substitution and Elimination Reactions

9.1 THE GENERAL REACTION

As described in Section 8.14, an **elimination reaction** occurs when a proton and the leaving group are lost from adjacent carbons, resulting in the formation of a double bond. In general, the reaction can be represented as



(Note that this general equation is not intended to indicate the order in which these bonds are made or broken; that is, it is not intended to show the mechanism for the reaction.) If the carbon bonded to the leaving group is

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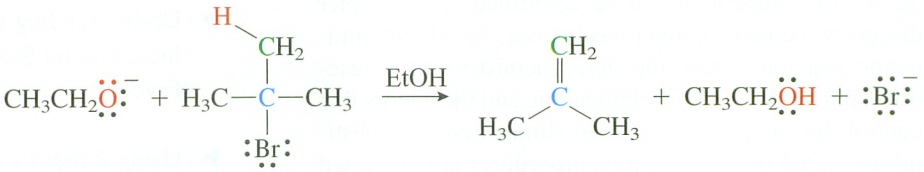
called carbon 1, then the proton is lost from carbon 2. The reaction is therefore termed a **1,2-elimination.** (Alternatively, because the carbon attached to the functional group is called the α-carbon and the adjacent carbon is the β-carbon, the reaction can also be called a ***β*-elimination.**)

As was the case with nucleophilic substitution reactions, there are two mechanisms for these elimination reactions. One mechanism is concerted and parallels the S_N2 reaction, whereas the other involves the formation of a carbocation intermediate and parallels the S_N1 reaction. The concerted mechanism is discussed first.

9.2 Bimolecular Elimination

The reaction of ethoxide ion with *tert*-butyl bromide in ethanol as solvent results in the formation of the elimination product 2-methylpropene.

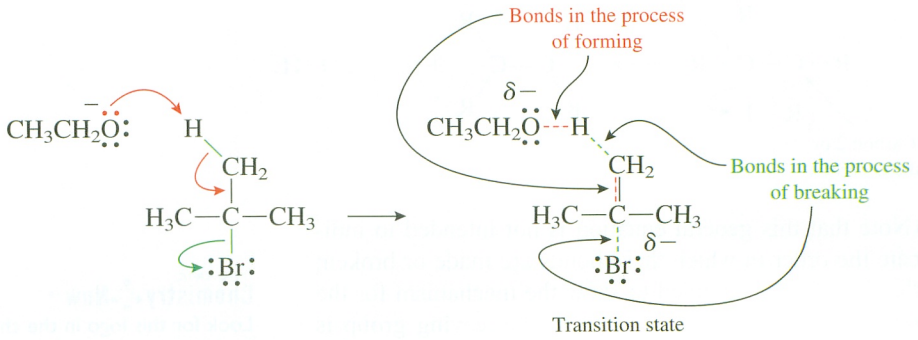


This reaction follows the second-order rate law:

$$\text{rate} = k[\text{EtO}^-][t\text{-BuBr}]$$

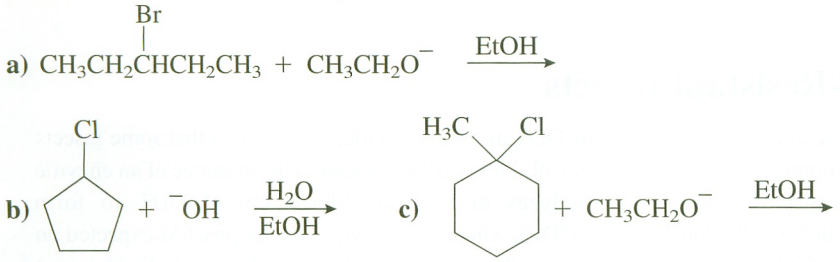
The rate law is consistent with a concerted or one-step mechanism. Because two species, ethoxide ion and *tert*-butyl bromide, react in this step, the reaction is described as a **bimolecular elimination** or an **E2 reaction.** This reaction is quite common when alkyl halides are treated with strong bases. Because many nucleophiles are also quite basic, the E2 reaction often competes with the S_N2 reaction.

The mechanism of this concerted reaction involves breaking and forming several bonds simultaneously. The base begins to form a bond to the hydrogen, the carbon–hydrogen bond begins to break, the carbon–bromine bond also begins to break, and the pi bond begins to form. The overall process and the transition state can be represented as follows:



PROBLEM 9.1

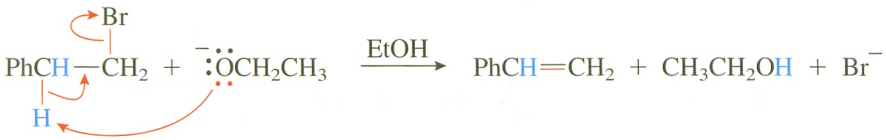
Show the elimination products of these reactions:



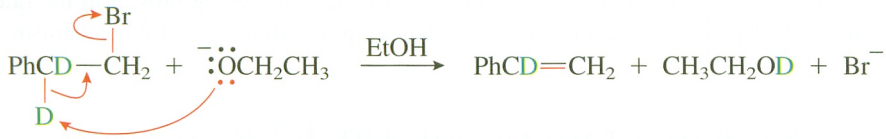
What evidence is available to support the mechanism shown for the E2 reaction? The experimental rate law tells us that both the base and the alkyl halide are present in the transition state or in some step prior to the transition state. Many other experimental techniques can be used to test whether a mechanism that has been proposed for a reaction is the one that is most plausible. Several of these employ the substitution of a less common isotope for one or more of the atoms of the compound. For example, a normal hydrogen atom ($^{1}_{1}H$) can be replaced with a deuterium atom ($^{2}_{1}H$ or D) or a tritium ($^{3}_{1}H$ or T) atom. Or a normal carbon ($^{12}_{6}C$) atom can be replaced with a $^{13}_{6}C$ or $^{14}_{6}C$ atom. Because isotopic substitution has only a very small effect on the chemical behavior of a compound, the isotopically modified compound undergoes the same reactions and follows the same mechanisms as its unmodified counterpart. In one type of experiment, the isotope is used to trace the fate of the labeled atom as the reactant is converted to the product.

In another type of experiment, the effect of the isotope on the reaction rate is studied. Because of their different molecular masses, isotopes can have a small effect on the rate of a reaction. Because deuterium is twice as massive as a normal hydrogen, the bond dissociation energy for a C—D bond is about 1.2 kcal/mol (5.0 kJ/mol) larger than that for a C—H bond. If this bond is broken during the rate-determining step of the reaction, then replacing the hydrogen with a deuterium can result in a significant decrease in the reaction rate because more energy must be supplied to break the stronger C—D bond. This is called a kinetic isotope effect.

As an example, comparison of the experimental rate of this elimination reaction



to the rate of the reaction of the deuterated analog

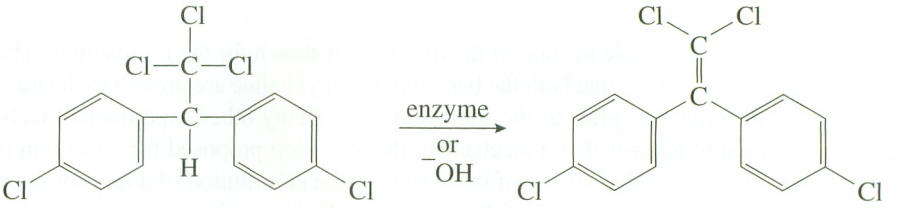


showed that the deuterated compound reacted more slowly by a factor of 7.1. This is a large deuterium isotope effect and indicates that the C—D bond is being broken during the rate-determining step of this reaction. Although this experimental result does not

Focus On Biological Chemistry

DDT-Resistant Insects

Some time after the introduction of DDT as an insecticide, it was found that some insects were becoming resistant to the chemical. This was later traced to the presence of an enzyme in the resistant insects that catalyzes the dehydrochlorination of DDT to form dichlorodiphenyldichloroethylene (DDE), which is not toxic to the insects. (As expected on the basis of its structure, DDT also gives this elimination reaction when treated with base.)

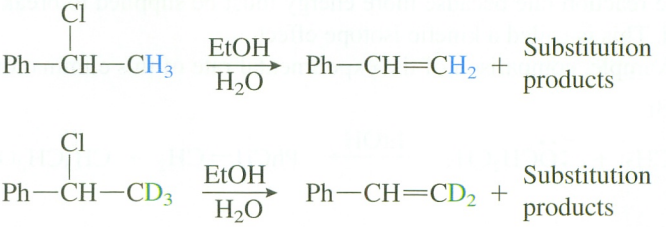


DDT DDE

The presence of this enzyme is a recessive trait that was present in a small part of the insect population before the introduction of DDT. When the insecticide killed the majority of the population that did not possess the enzyme, the insects that had the enzyme became dominant, a classic example of natural selection. (Or is it "unnatural selection" in this case?)

prove that the mechanism is E2 (an experiment cannot prove a mechanism but can disprove it), it is consistent with this mechanism.

As a contrasting example, these reactions occur at nearly identical rates:



The fact that the reaction of the undeuterated compound is only 1.2 times faster than that of the deuterated analog indicates that the C—D bond is not being broken in the rate-determining step. Therefore, this reaction cannot be proceeding by an E2 mechanism.

9.3 Stereochemistry of the E2 Reaction

Reactions such as the E2 elimination, in which several bonds are made and broken simultaneously, usually have strict requirements for the stereochemical relationship of these bonds as the reaction proceeds. These **stereoelectronic requirements** occur because the

orbitals that are going to form the new bonds must begin to overlap at the very start of the reaction. As the reaction proceeds, this overlap increases and provides significant stabilization in the transition state to help offset the energy cost of breaking the other bonds.

In the case of the E2 reaction the carbon sp^3 orbital of the carbon–hydrogen sigma bond and the carbon sp^3 orbital of the carbon-leaving group sigma bond must begin to overlap to form the pi bond. This requires that these two sigma bonds lie in the same plane; they must be coplanar. The two bonds may be on the same side of the C—C bond (**syn-periplanar conformation**) or on opposite sides of the C—C bond (**anti-periplanar conformation**). These conformations are shown in Figure 9.1. As the reaction proceeds, the bonds to the hydrogen and the leaving group begin to lengthen, and the two carbons begin to change hybridization from sp^3 to sp^2. The orbitals that are initially bonded to the hydrogen and the leaving group change from sp^3 orbitals to the p orbitals of the pi bond.

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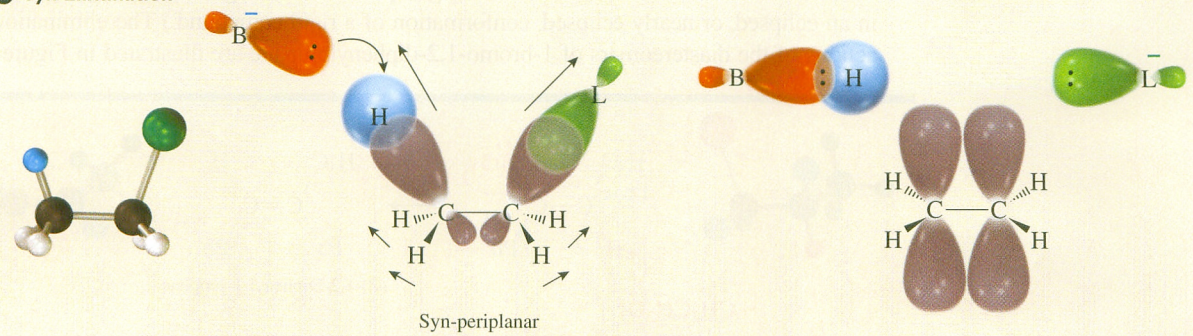
Click *Mechanisms in Motion* to view the **E2 Mechanism.**

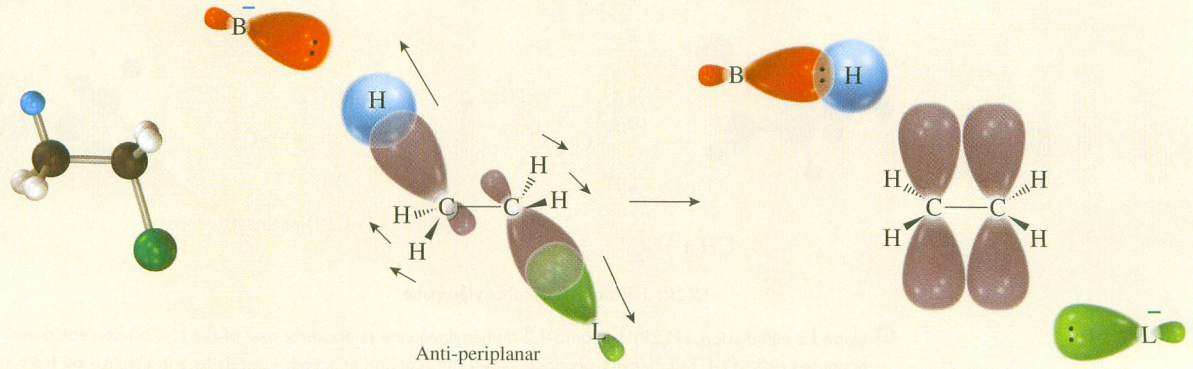
ⓐ Syn Elimination



Syn-periplanar

In the syn-periplanar conformation, the C—H and C—L sigma bonds are coplanar and on the same side of the C—C bond. As the bonds to the hydrogen and the leaving group start to break, the hybridization at each carbon begins to change to sp^2, and the two sp^3 orbitals, which have some pi-type overlap initially, change to the p orbitals of the pi bond.

ⓑ Anti Elimination



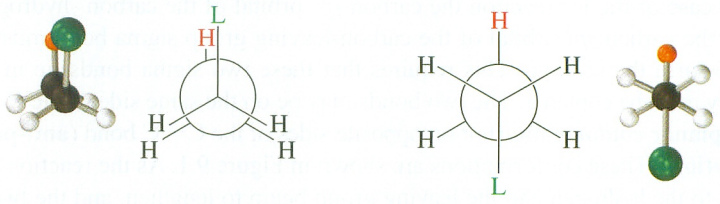
Anti-periplanar

In the anti-periplanar conformation, the C—H and C—L sigma bonds are coplanar but on opposite sides of the C—C bond. Again, as the bonds break, the carbons change hybridization, and the sp^3 orbitals change to the parallel p orbitals of the pi bond.

Figure 9.1

MECHANISM OF E2 ELIMINATION FROM ⓐ SYN-PERIPLANAR AND ⓑ ANTI-PERIPLANAR CONFORMATIONS.

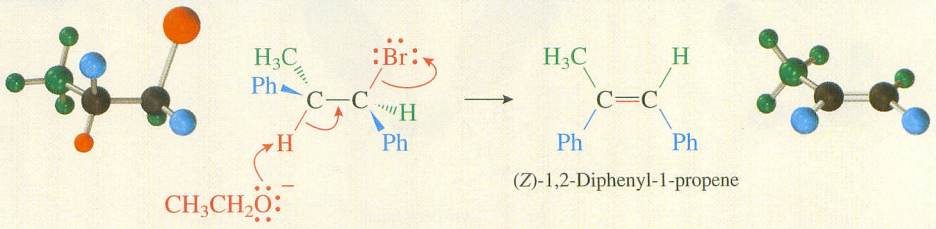
Closer examination reveals that the syn-periplanar conformation has all the bonds eclipsed, whereas the anti-periplanar conformation has these bonds staggered, as shown in the following Newman projections:



Syn-periplanar conformation

Anti-periplanar conformation

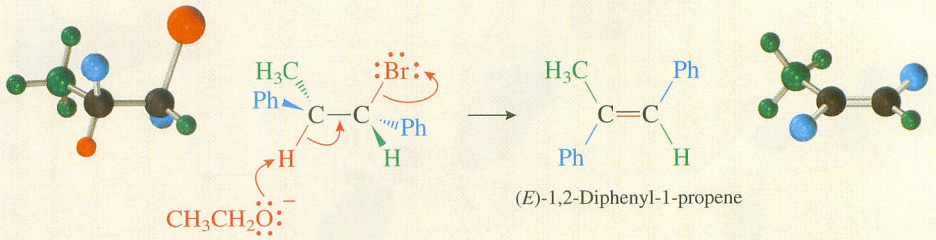
The anti-periplanar conformation is more stable because it is staggered rather than eclipsed. Therefore, anti elimination is preferred in the E2 reaction. (Syn elimination is much less common but does occur when the leaving group and the hydrogen are held syn-periplanar in an eclipsed, or nearly eclipsed, conformation of a rigid compound.) The elimination reactions of the diastereomers of 1-bromo-1,2-diphenylpropane are illustrated in Figure 9.2.



(1*R*,2*R*)-1-Bromo-1,2-diphenylpropane

(*Z*)-1,2-Diphenyl-1-propene

a Upon E2 elimination, (1*R*,2*R*)-1-bromo-1,2-diphenylpropane produces only (*Z*)-1,2-diphenylpropene. This result demonstrates that the reaction occurs entirely from the anti-periplanar conformation shown. The enantiomer of this compound, (1*S*,2*S*)-1-bromo-1,2-diphenylpropane, also produces only the (*Z*)-alkene when it undergoes an E2 elimination reaction. (To simplify viewing, the phenyl groups are shown as single blue atoms in the ball-and-stick models.)



(1*S*,2*R*)-1-Bromo-1,2-diphenylpropane

(*E*)-1,2-Diphenyl-1-propene

b Upon E2 elimination, (1*S*,2*R*)-1-bromo-1,2-diphenylpropane (a diastereomer of the (1*R*,2*R*)-stereoisomer) produces only (*E*)-1,2-diphenyl-1-propene. Again the reaction proceeds entirely by anti elimination from the conformation shown. The enantiomer of this compound also produces only the (*E*)-alkene. (To simplify viewing, the phenyl groups are shown as single blue atoms in the ball-and-stick models.)

Active Figure 9.2

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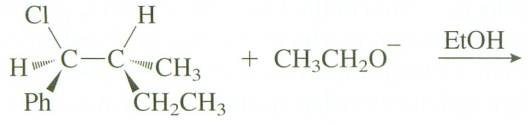
MECHANISM AND STEREOCHEMISTRY OF THE E2 ELIMINATION REACTIONS OF THE DIASTEREOMERS OF 1-BROMO-1,2-DIPHENYL-PROPANE TO PRODUCE (a) THE (*Z*) STEREOISOMER AND (b) THE (*E*) STEREOISOMER OF 1,2-DIPHENYL-1-PROPENE. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

The preference for anti elimination results in the (1*R*,2*R*)-diastereomer of the bromide producing only the (*Z*)-isomer of the alkene, and the (1*S*,2*R*)-bromide producing only the (*E*)-alkene.

PRACTICE PROBLEM 9.1

Show the stereochemistry of the product of this elimination reaction:

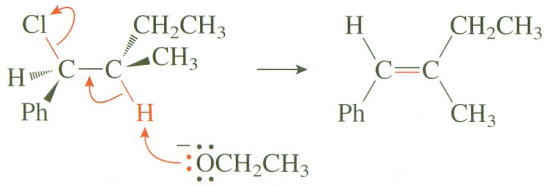


Strategy

First identify the H and the leaving group (L) that are eliminated in the reaction. Remember that E2 elimination requires a conformation that has the H and the L in an anti-periplanar geometry. If they are not in such a conformation as drawn, redraw the molecule so that they are. When the elimination occurs, groups that are on the same side of the plane defined by H-C-C-L in the reactant become cis in the product alkene.

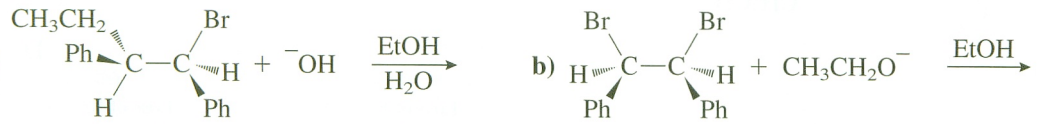
Solution

As originally shown, the H and the Cl that are eliminated are syn, so a rotation of 180° about the C—C bond is needed. Anti elimination then gives the (*E*)-isomer of the product.



PROBLEM 9.2

Show the products, including stereochemistry, of these elimination reactions.

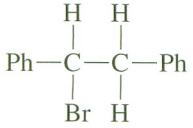


PROBLEM 9.3

What product would be expected from the elimination reaction of (1*R*,2*S*)-1-bromo-1,2-diphenylpropane using sodium ethoxide in ethanol as the solvent?

PROBLEM 9.4

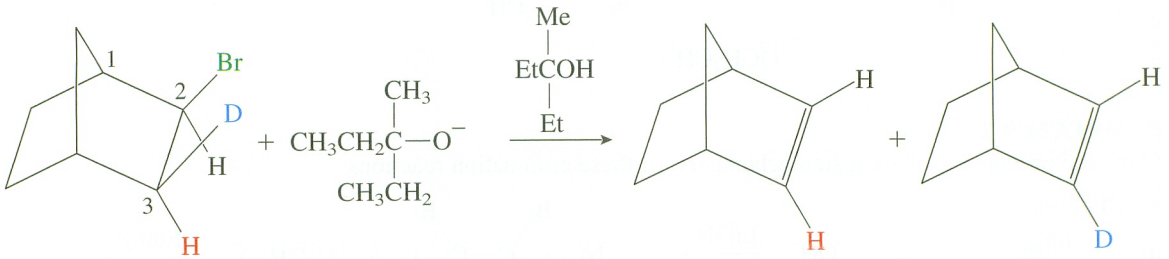
Both cis and trans alkenes can be formed from this compound by anti elimination. Draw a Newman projection of the conformation required to form each of these products and, on the basis of these projections, predict which of these products would be formed in larger amounts.

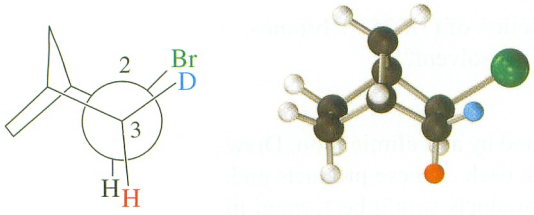


Syn elimination is less favorable than anti elimination because the molecule must be in a higher-energy eclipsed conformation for syn elimination to occur. However, syn elimination does occur in rigid molecules where the leaving group and the hydrogen are held in an eclipsed conformation. For example, the bicyclic compound shown in Figure 9.3 is very rigid. As can be seen in the Newman projection down the C-2—C-3 bond, the Br and the D are eclipsed. (Examination of a model will help you see how rigid this molecule is and that the Br and D groups are eclipsed.) Deuterium is used as a label to enable syn elimination to be distinguished from anti elimination. Syn elimination results in the loss of the D and the Br, so the product contains no deuterium, whereas anti elimination results in the loss of H and Br, so the product still contains the deuterium. In the presence of a strong base, 94% of the product alkene contains no deuterium and therefore has resulted from syn elimination.

Not much of the "anti elimination" product is formed because the hydrogen on C-3 and the bromine are not in an anti relationship (the dihedral angle between them is 120°). Thus, elimination of this hydrogen and the bromine occurs with poor orbital overlap at the early stages of the reaction.

For anti elimination to occur in a cyclohexane ring, the leaving group and the hydrogen must be trans. Furthermore, they will be anti-periplanar only in the conformation where both are axial. This ***trans*-diaxial elimination** is illustrated in Figure 9.4 for menthyl chloride and in Figure 9.5 for neomenthyl chloride. These substituted cyclohexyl chlorides are diastereomers. They differ only in the configuration of the chlorine substituent. However, as shown in Figures 9.4 and 9.5, this difference leads to dramatically different behavior when these two compounds are treated with the strong base ethoxide ion.

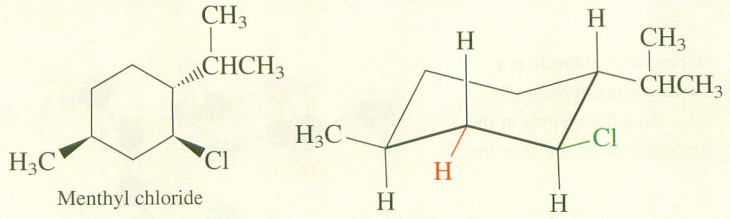




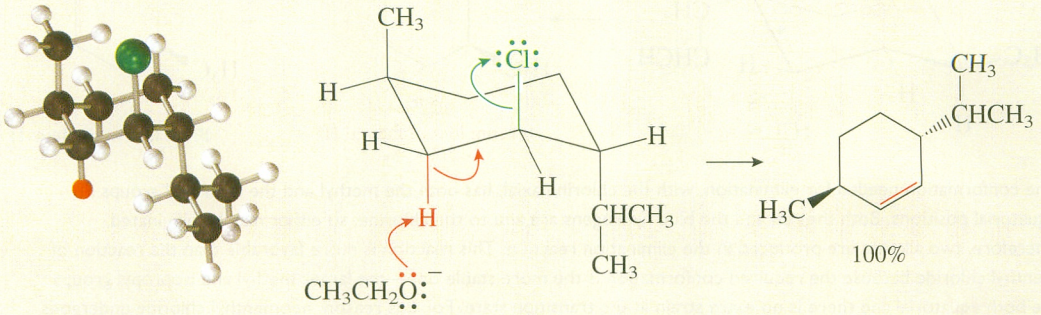
Newman projection

Figure 9.3

SYN ELIMINATION IN A RIGID MOLECULE.



a The most stable chair conformation of menthyl chloride has all three substituents equatorial. However, elimination cannot occur from this conformation because the chlorine is not axial.



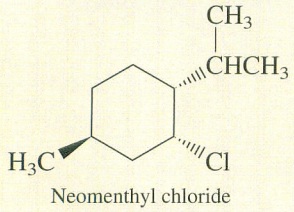
b The other chair conformation is much less stable because all three substituents are axial. It constitutes only a small percentage of the conformational equilibrium (about 0.06%). Anti elimination can occur from this conformation because it has the chlorine and a hydrogen in a *trans*-diaxial arrangement. Only the red hydrogen is anti to the chlorine, so it is the only one that can be involved in the elimination reaction. This results in the production of a single alkene. The reaction is relatively slow because the activation energy includes at least part of the energy needed to ring-flip to this less stable conformation.

Figure 9.4

MECHANISM AND STEROCHEMISTRY OF THE E2 ELIMINATION REACTION OF MENTHYL CHLORIDE.

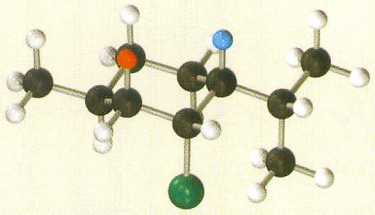
Analysis of the elimination reactions of these cyclohexane derivatives must be done with care. First, the chair conformation with the chlorine axial must be examined. In the case of menthyl chloride (see Figure 9.4) this conformation has all three groups axial and is much less stable than the ring-flipped conformation. However, elimination must occur from this conformation because only here are a hydrogen and the chlorine anti-periplanar. The reaction has a higher activation energy and is relatively slow because some of the strain energy of the higher-energy conformation is still present in the transition state. In addition, the reactive conformation has a single hydrogen in the required anti-periplanar relationship to the chlorine. Only this hydrogen is lost in the elimination reaction, and therefore, a single alkene is produced.

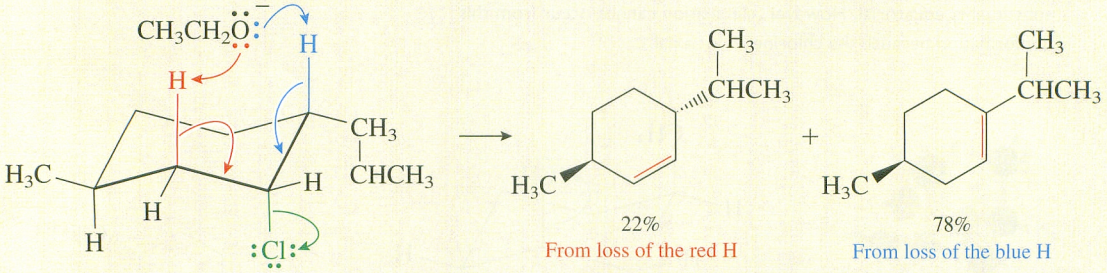
In contrast, neomenthyl chloride, with the opposite configuration at the carbon bearing the chlorine, has both the isopropyl and the methyl groups equatorial in the reactive conformation, with the chlorine axial (see Figure 9.5). Because both of these groups have larger axial strain energies than chlorine (see Table 6.2), the reactive conformation is the more stable one. There is less steric strain in the transition state for elimination,



Neomenthyl chloride

Neomenthyl chloride is a diastereomer of menthyl chloride, differing only in the configuration of the chlorine.





The conformation needed for elimination, with the chlorine axial, has both the methyl and the isopropyl groups in equatorial positions. Both the red and the blue hydrogens are anti to the chlorine, so either may be eliminated. Therefore, two alkenes are produced in the elimination reaction. This reaction is more favorable than the reaction of menthyl chloride because the required conformation is the more stable one—the larger methyl and isopropyl groups are both equatorial and there is no extra strain in the transition state. For this reason, neomenthyl chloride undergoes elimination about 40 times faster than menthyl chloride.

Figure 9.5

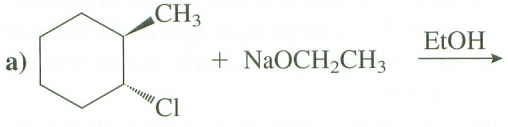
MECHANISM AND STEREOCHEMISTRY OF THE E2 ELIMINATION REACTION OF NEOMENTHYL CHLORIDE.

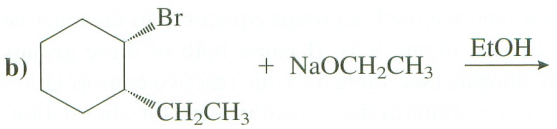
so the activation energy is smaller. This results in neomenthyl chloride reacting about 40 times faster than menthyl chloride.

As can be seen in Figure 9.5, neomenthyl chloride has two hydrogens in an antiperiplanar geometry with the chlorine. Either of these hydrogens can be lost in the elimination reaction, resulting in the formation of two alkenes. (All of the examples presented up to this point were chosen so that only one alkene could be formed.) Let's now address this issue of the direction of the elimination and learn how to predict which will be the major product when more than one alkene can be formed.

PROBLEM 9.5

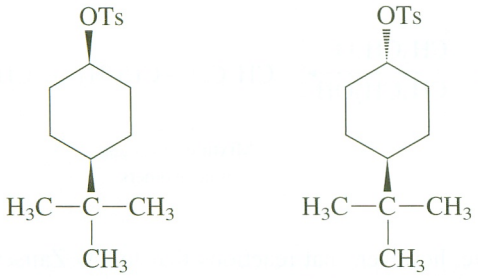
Show the products of these elimination reactions:





PROBLEM 9.6

Explain why one of these compounds reacts readily by an E2 mechanism when treated with sodium ethoxide in ethanol but the other does not:



9.4 DIRECTION OF ELIMINATION

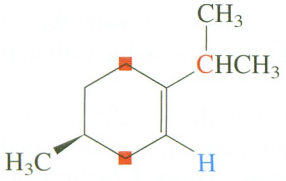
Chapter 8 discussed the stereochemistry of substitution reactions—that is, what happened to the stereochemistry when the reaction occurred at a carbon chirality center. This section discusses the **regiochemistry** of the elimination reaction—that is, what happens when a reaction can produce two or more structural isomers. The structural isomers that can often be produced in elimination reactions have the double bond in different positions. As shown in Figure 9.5, elimination of hydrogen chloride from neomenthyl chloride produces two structural isomers but in unequal amounts.

It is possible to predict which product will be formed in larger amounts in these reactions. Most E2 elimination reactions follow **Zaitsev's rule:**

ZAITSEV'S RULE

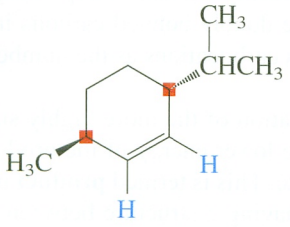
The major alkene product is the one with more alkyl groups on the carbons of the double bond (the more highly substituted product).

In the case of neomenthyl chloride the major product has three carbon groups and one hydrogen as the four groups bonded to the carbons of the double bond, whereas the minor product has two carbon groups and two hydrogens so bonded.



Major product (78%)

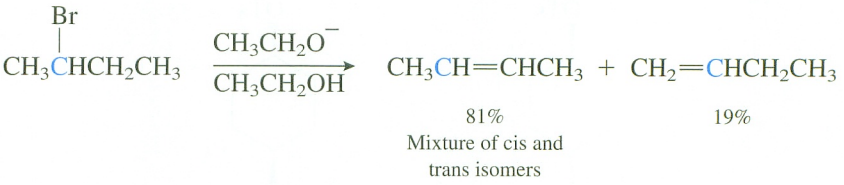
This product has three carbons and one hydrogen bonded to the carbons of the double bond.



Minor product (22%)

This product has two carbons and two hydrogens bonded to the carbons of the double bond.

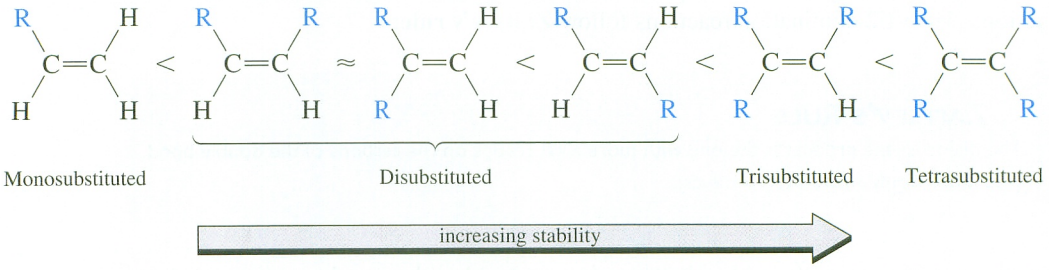
Another example is provided by the elimination reaction of 2-bromobutane using ethoxide ion as the base. The major product is the more highly substituted alkene.



It is important to note, however, that reactions that follow Zaitsev's rule still produce significant amounts of the less highly substituted product.

Zaitsev's rule is an **empirical rule;** that is, it is based on experimental observations, not theory. It was first proposed in 1875, when there was little theoretical basis for any part of organic chemistry. Now that we have learned about mechanisms, we know that the transition state leading to the more highly substituted product must be of lower energy than the one leading to the less highly substituted product. Let's examine why this is the case.

A number of studies using heats of reaction have shown that a more highly substituted alkene is more stable than a less highly substituted alkene. Therefore, the general order of stability for compounds containing carbon–carbon double bonds is



Although there is still some debate, the increasing stabilization is postulated to result from the increasing amount of hyperconjugation that can occur as the number of alkyl groups on the doubly bonded carbons increases. This is the same type of interaction that stabilizes carbocations as the number of alkyl groups on the carbon increases (see Section 8.7).

The formation of the more highly substituted product in elimination reactions results from the lower energy of the product being reflected in a somewhat more stable transition state. This is termed **product development control.** In this reaction the transition state, having a structure between the reactant and the product, is stabilized by the same factors that stabilize the product, although the amount of stabilization is less. This is illustrated in Figure 9.6, an energy versus reaction progress diagram for the elimination reaction of 2-bromobutane. The more stable alkene, 2-butene, is the major product (81%), but because the energy difference between the transition states for the

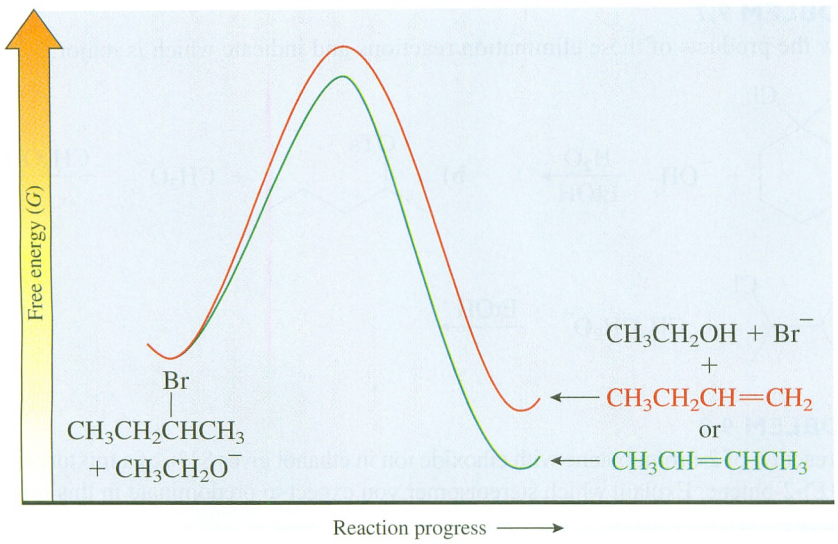


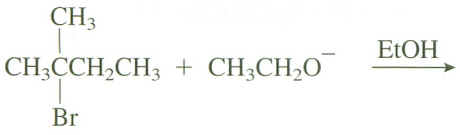
Figure 9.6

FREE ENERGY VERSUS REACTION PROGRESS DIAGRAM FOR THE ELIMINATION REACTION OF 2-BROMOBUTANE.

two products is not very large, a significant amount (19%) of the minor product, 1-butene, is also formed.

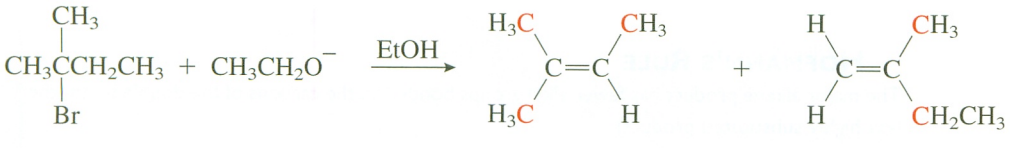
PRACTICE PROBLEM 9.2

Show the products of this elimination reaction and explain which is the major product:



Solution

Two alkenes are expected to be formed in this reaction. According to Zaitsev's rule, the more highly substituted alkene is the major product.



Major

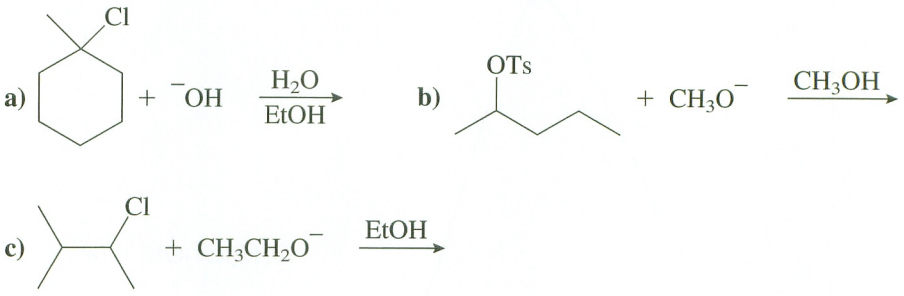
The major product is a trisubstituted alkene with three alkyl groups on the carbons of the double bond.

Minor

The minor product is a disubstituted alkene with two alkyl groups on the carbons of the double bond.

PROBLEM 9.7

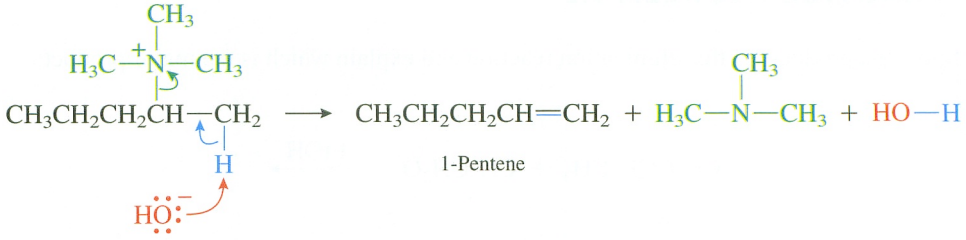
Show the products of these elimination reactions and indicate which is major:



PROBLEM 9.8

The reaction of 2-bromobutane with ethoxide ion in ethanol gives 81% of a mixture of (*Z*)- and (*E*)-2-butene. Explain which stereoisomer you expect to predominate in this mixture.

Although most E2 reactions follow Zaitsev's rule, there are some exceptions. One major exception is a reaction known as the **Hofmann elimination.** Compounds that can undergo this reaction have a quaternary nitrogen atom—that is, a nitrogen that is positively charged because it is bonded to four alkyl groups. The nitrogen, with three of the alkyl groups, acts as a leaving group when the ion is heated in the presence of a base such as hydroxide ion. An example of the Hofmann elimination reaction is provided in the following equation:



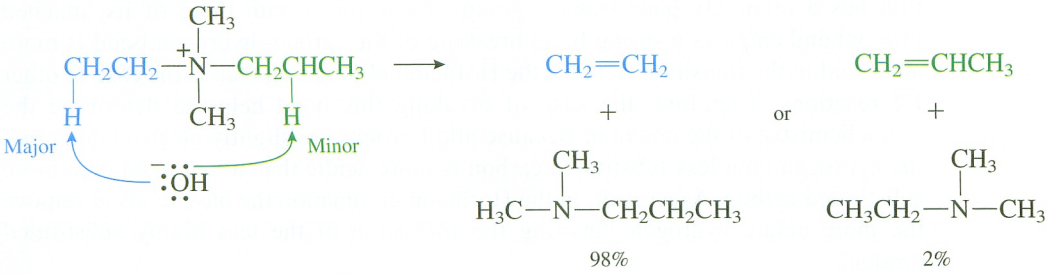
In this example, 1-pentene and 2-pentene are possible products. The reaction produces almost exclusively 1-pentene, the less highly substituted product. This elimination reaction follows **Hofmann's rule:**

> **HOFMANN'S RULE**
>
> The major alkene product has fewer alkyl groups bonded to the carbons of the double bond (the less highly substituted product).

As exemplified by the high yield of 1-pentene in this reaction, the preference for the less highly substituted product is often quite strong.

In the previous example the elimination could occur only in the pentyl group because the other three substituents on the nitrogen are methyl groups, which do not have β-carbons. However, if more than one of the alkyl groups bonded to the nitrogen is larger than methyl, then elimination can, in principle, involve any of these groups.

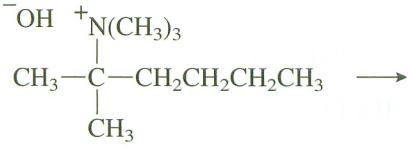
Again, Hofmann's rule predicts that the major pathway will be the one that produces the less highly substituted alkene. An example is shown in the following equation:



In this case a β-hydrogen (a hydrogen on the β-carbon) could be lost from either the ethyl or the propyl group. In accord with Hofmann's rule the less highly substituted alkene, ethene, is found to be the major product.

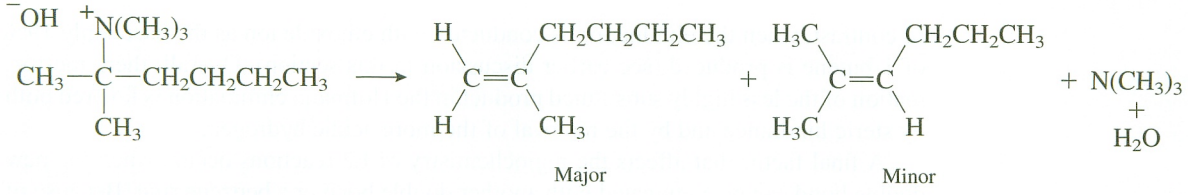
PRACTICE PROBLEM 9.3

Show the products of this reaction and explain which is the major product:



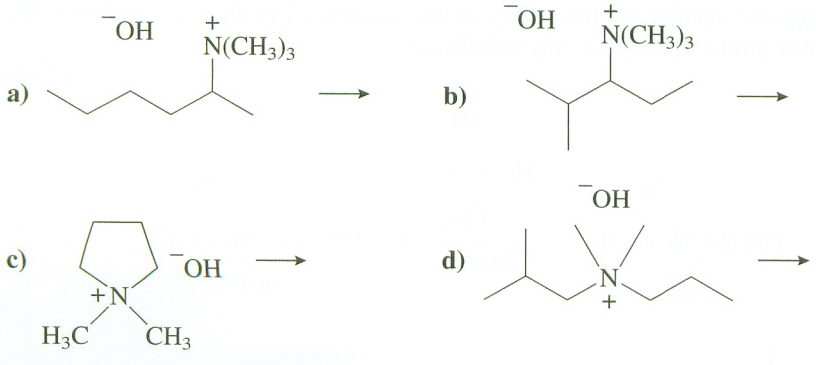
Solution

This elimination reaction follows Hofmann's rule, so the less substituted alkene should be the major product.



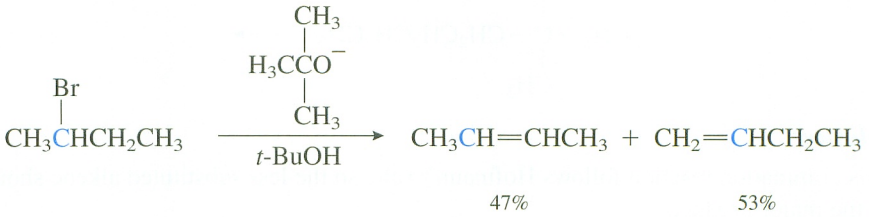
PROBLEM 9.9

Show the products of these reactions and indicate which is major:



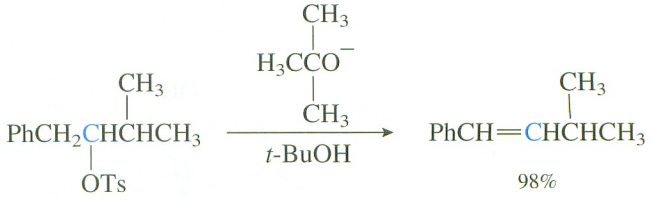
The reasons why the Hofmann elimination produces more of the less highly substituted alkene (which is also the less stable alkene) are complex. Because the reaction has a relatively poor leaving group (the nitrogen with three of its attached groups) and employs a strong base, breaking of the carbon–hydrogen bond is more advanced in the transition state for the Hofmann elimination than is the case in other E2 reactions. Therefore, the ease of breaking this bond helps to determine the regiochemistry of the reaction. Because alkyl groups are slightly electron donating, the hydrogen on a less substituted carbon is more acidic than a hydrogen on a more substituted carbon. As a result, in the Hofmann elimination the base tends to remove the more acidic hydrogen, favoring the formation of the less highly substituted product.

Steric effects are also postulated to be important in determining the regiochemistry of this reaction. It is proposed that the large size of the leaving group in the Hofmann elimination (a tertiary amine) causes the base to attack the less sterically hindered hydrogen—one on the carbon with fewer alkyl groups. Steric effects can be important in reactions other than the Hofmann elimination also. For example, the elimination reaction of 2-bromobutane using *tert*-butoxide ion as the base, an E2 reaction employing a strong, sterically hindered base, gives more 1-butene than 2-butene, as shown in the following equation:



In contrast, when the elimination is conducted with ethoxide ion as the base, only 19% of 1-butene is produced (see earlier discussion in this section). Overall, then, the formation of the less highly substituted product in the Hofmann elimination is favored both by steric hindrance and by the removal of the more acidic hydrogen.

A final factor that affects the regiochemistry of E2 reactions occurs when the new double bond can be conjugated with another double bond or a benzene ring. Because of resonance stabilization, a conjugated product is considerably more stable than a nonconjugated one. The partial development of conjugation in the transition state results in enough stabilization that the conjugated product is always the major one. For example, the following elimination produces 98% of the conjugated product, even though the other possible product is more highly substituted:

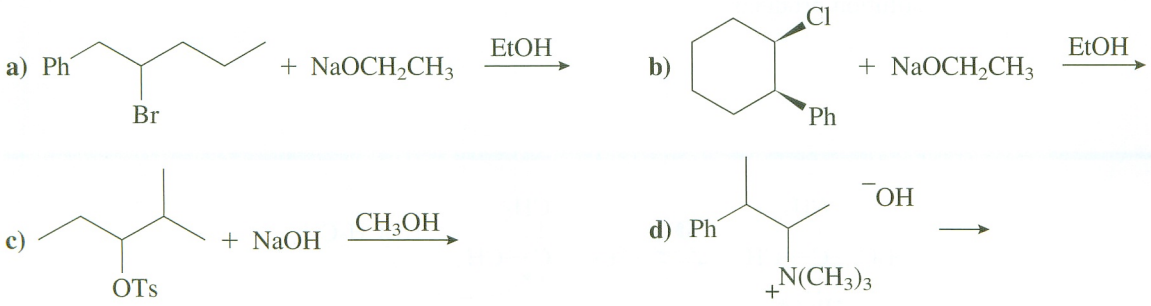


In summary, the regiochemistry of E2 reactions can be predicted by using the following rules:

1. Most E2 reactions follow Zaitsev's rule; the more highly substituted alkene is the major product.
2. Hofmann eliminations follow Hofmann's rule; the less highly substituted product is the major product.
3. A conjugated alkene is always preferred to an unconjugated alkene.

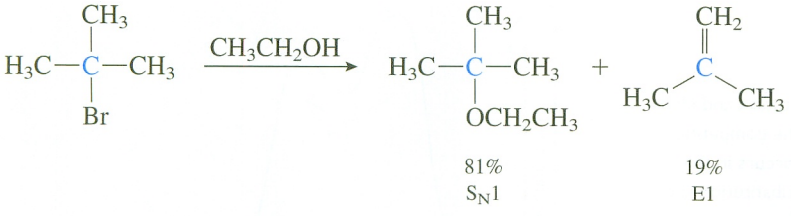
PROBLEM 9.10

Show the major products of these elimination reactions:



9.5 Unimolecular Elimination

The reaction of *tert*-butyl bromide with ethoxide ion, shown at the beginning of Section 9.2, resulted in the formation of 2-methylpropene in an E2 reaction. If ethoxide ion is not present in the reaction, E2 elimination is greatly slowed, and both substitution and elimination products are formed.



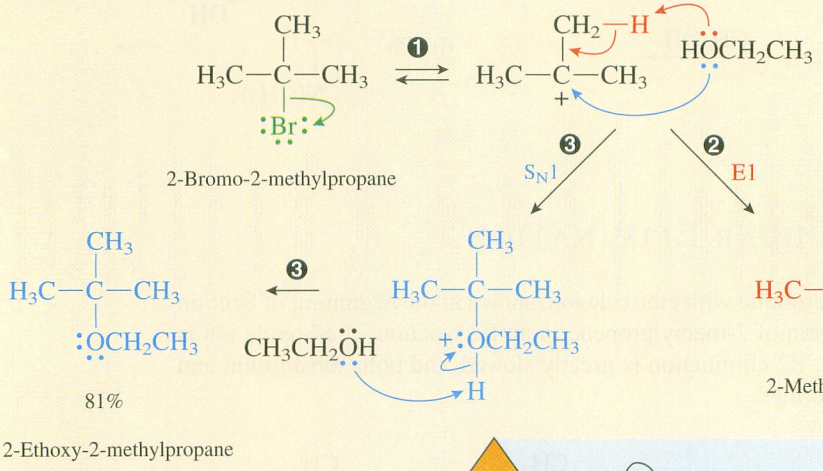
The rate of appearance of both products is found to follow the first-order rate law:

$$\text{rate} = k[t\text{-BuBr}]$$

It is easy to recognize that the substitution product is formed by an S_N1 mechanism, because the starting alkyl bromide is tertiary. Because the elimination reaction follows the same rate law, its rate-determining step, like that of the S_N1 reaction, must also involve only a molecule of *tert*-butyl bromide. Therefore, the elimination reaction is described as a **unimolecular elimination** or an **E1 reaction.**

ORGANIC Chemistry Now™
Click *Mechanisms in Motion* to view the **E1 Mechanism.**

The E1 reaction follows the same rate law as the S_N1 reaction because both mechanisms have the same rate-determining step: the formation of the carbocation, as shown in Figure 9.7. In the second step of the mechanism the ethanol can react with the carbocation as a nucleophile to give the S_N1 product or as a base to give the E1 product. Under these particular conditions the transition state (for the second step) leading to substitution is slightly lower in energy than the transition state leading to elimination, so the substitution product is the major one. If an elimination is possible (if there is a β-hydrogen), then some elimination product always accompanies the substitution product in S_N1 reactions. Because the amount of elimination is difficult to control, this detracts from the usefulness of these reactions to prepare other compounds. In addition, carbocation rearrangements (see Section 8.14) may lead to rearranged elimination products as well as rearranged substitution products.



❶ The rate-determining step for both substitution and elimination is the formation of the carbocation. The competition between ❷ elimination and ❸ substitution occurs in the second step. The transition state leading to substitution is of slightly lower energy in this case, so more substitution product is formed than elimination product. The free energy versus reaction progress diagram is shown on the right.

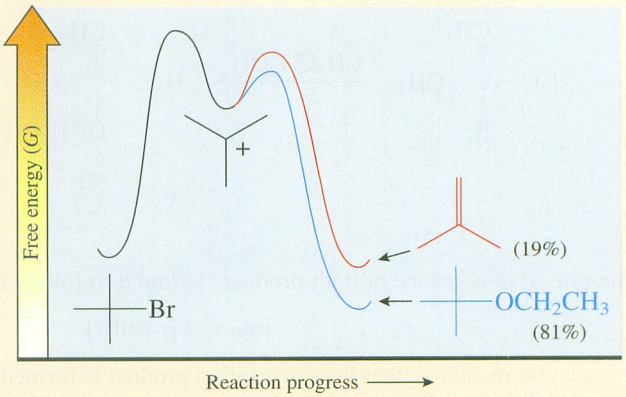
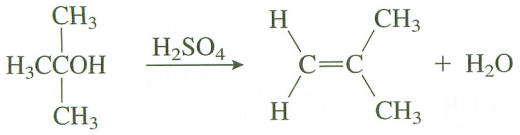


Figure 9.7

MECHANISM OF THE S_N1 SUBSTITUTION AND E1 ELIMINATION REACTIONS OF *TERT*-BUTYL BROMIDE (2-BROMO-2-METHYLPROPANE).

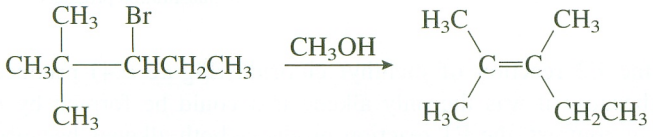
PROBLEM 9.11

When 2-methyl-2-propanol is treated with sulfuric acid, 2-methylpropene is formed. Show all of the steps in the mechanism for this reaction. Don't forget to use curved arrows to show the movement of electrons in each step of the mechanism.



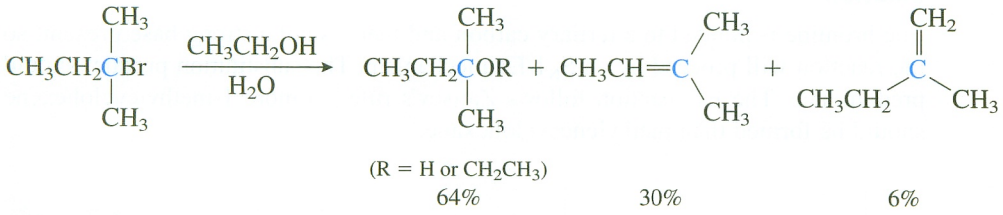
PROBLEM 9.12

Show all of the steps in the mechanism for this reaction. What other products would you expect to be formed?



9.6 REGIOCHEMISTRY AND STEREOCHEMISTRY OF THE E1 REACTION

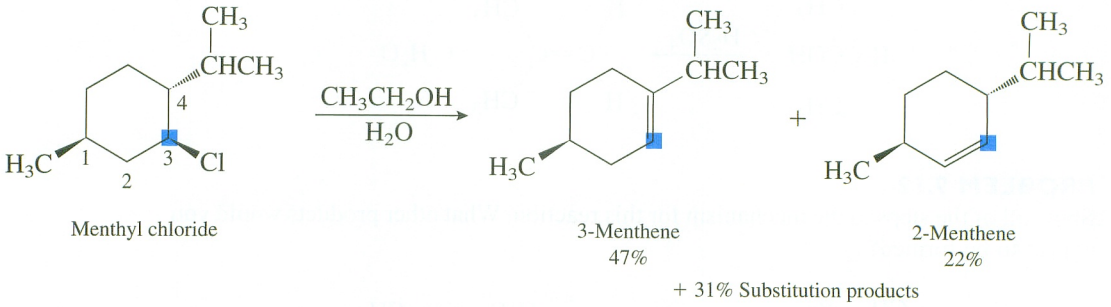
When regioisomers are possible in an E1 reaction, the product distribution is found to follow Zaitsev's rule. The reaction of 2-bromo-2-methylbutane under S_N1/E1 conditions (in a polar solvent mixture of ethanol and water with no good base or nucleophile present) gives 64% of the substitution products (water acts as the nucleophile to give an alcohol, or ethanol acts as a nucleophile to give an ether), 30% of the more highly substituted alkene, and 6% of the less highly substituted alkene.



As in the E2 reaction, the relative yields of the alkenes are under product development control—the more stable alkene predominates.

Unlike the E2 reaction, the relative stereochemistry of the leaving group and the hydrogen is not important in the E1 elimination reaction. In the first step of the reaction, the leaving group departs, producing a planar carbocation. Only at this point must the C—H bond be aligned parallel to the empty *p* orbital of the carbocation so that pi over-

lap can occur as the C—H bond begins to break. Therefore, *trans*-diaxial elimination is not required for E1 reactions involving cyclohexane rings. For example, the reaction of menthyl chloride under S_N1/E1 conditions gives the product distribution shown in the following equation:



Menthyl chloride

3-Menthene
47%

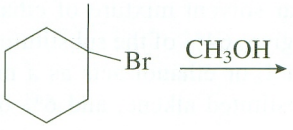
2-Menthene
22%

+ 31% Substitution products

Recall that the E2 reaction of menthyl chloride (Figure 9.4) produced 100% of 2-menthene because it was the only alkene that could be formed by *trans*-diaxial elimination. In contrast, the E1 reaction produces both alkenes because the stereochemistry is unimportant. The major product is 3-menthene (the more stable product), in accord with Zaitsev's rule.

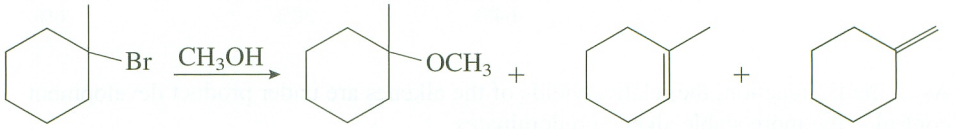
PRACTICE PROBLEM 9.4

Show the products of this reaction:



Solution

The bromine is bonded to a tertiary carbon and there is not a strong base present, so the reaction will proceed by an S_N1/E1 mechanism. The substitution product should predominate. The E1 reaction follows Zaitsev's rule, so more 1-methylcyclohexene should be formed than methylenecyclohexane.



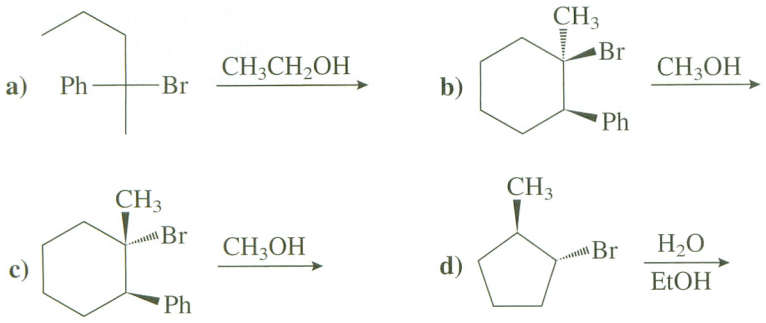
S_N1
major

1-Methylcyclohexene Methylenecyclohexane

E1
minor

PROBLEM 9.13

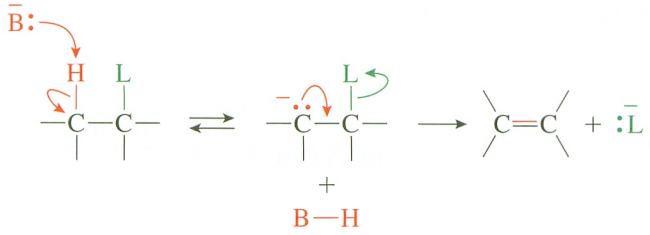
Show the products of these reactions:



Focus On

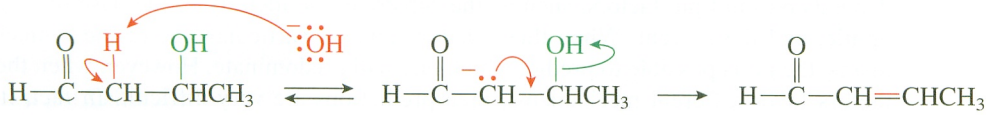
The E1cb Mechanism

In the E1 mechanism the bond to the leaving group breaks during the first step and the bond to the hydrogen breaks in a second step. In the E2 mechanism, both of these bonds break in a single step. There is a third possible mechanism in which the bond to the hydrogen breaks during the first step and the bond to the leaving group breaks in a second step, as illustrated in this equation:



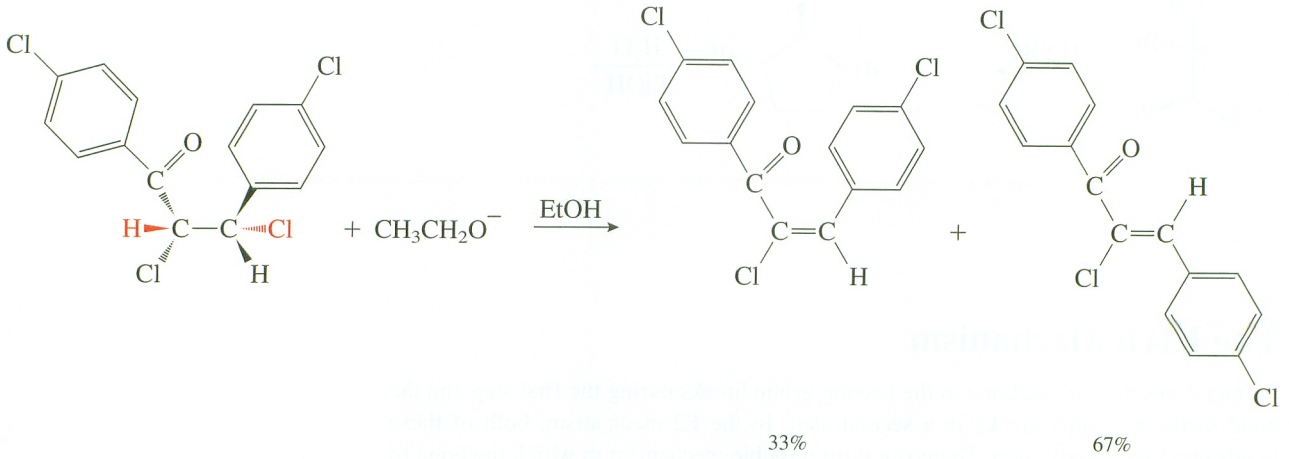
When this mechanism does occur, the second step often determines the rate. Because this step involves a unimolecular reaction of the conjugate base of the initial reactant, the mechanism is designated as elimination, unimolecular, conjugate base—or E1cb. The mechanism can be made more favorable by the presence of substituents that stabilize the intermediate carbanion. In addition, a poorer leaving group, which makes the second step less likely to be concerted with the first, also favors this mechanism.

The presence of a good anion-stabilizing group, such as a carbonyl group, attached to the carbon from which the proton is lost makes the E1cb mechanism quite favorable. In such situations, even a poor leaving group, such as hydroxide ion, can be eliminated as shown in the following equation:



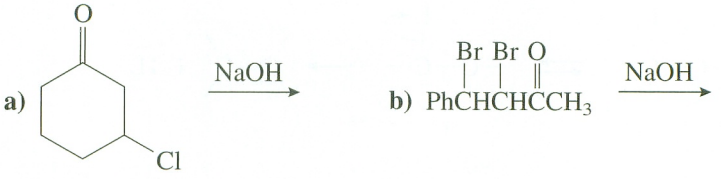
Continued

It is not always easy to distinguish an elimination reaction that is following the E1cb mechanism from one that follows the E2 pathway because the E1cb reaction usually exhibits second-order kinetics also. However, because the E1cb reaction is not concerted, there are no strict requirements concerning the stereochemistry of the reaction. In contrast to the preferred anti elimination that occurs in the E2 mechanism, E1cb reactions often produce a mixture of stereoisomers, as illustrated in the following equation:



PROBLEM 9.14

Show the products of these reactions:



9.7 THE COMPETITION BETWEEN ELIMINATION AND SUBSTITUTION

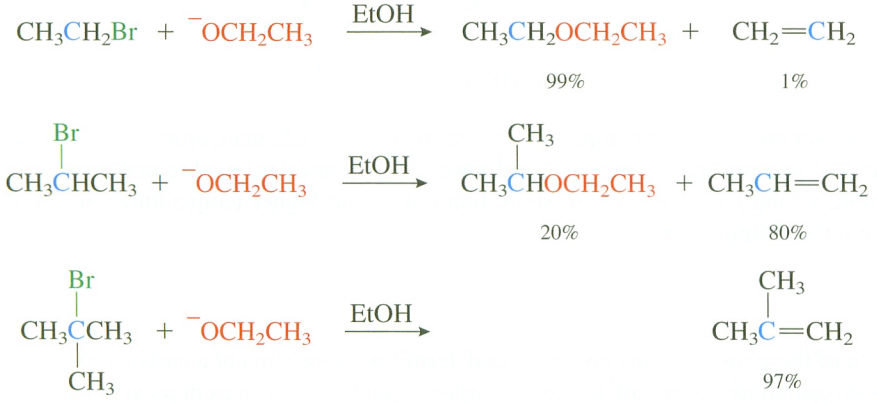
As the previous discussion has shown, there is a competition among four different mechanisms in these reactions: S_N1, S_N2, E1, and E2. The amount of each that occurs depends on multiple factors, such as the substrate, the identity of the base or nucleophile, and the solvent. When these factors favor a particular one of these mechanisms, then it is possible to predict which one will predominate. However, when these factors favor different mechanisms, then predictions are very difficult. In fact, it is

quite possible for several of the mechanisms to occur at the same time in a particular reaction. However, when these reactions are used in the laboratory, we are usually attempting to prepare a particular substitution product or a particular elimination product. It is usually possible to choose conditions carefully so that one mechanism is faster than the others and the yield of the desired substitution or elimination product is maximized.

The following generalizations provide a useful summary of the factors that control the competition among these mechanisms.

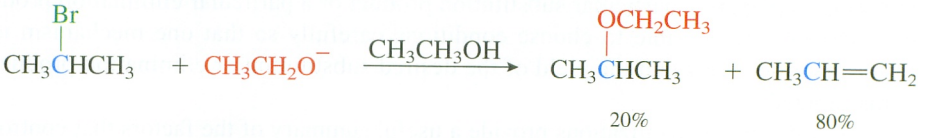
S_N2 and E2

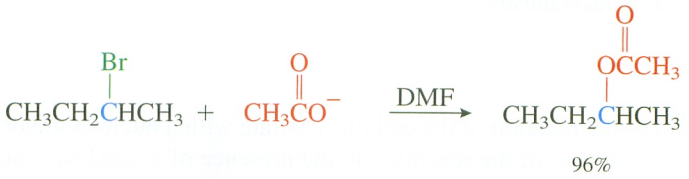
These two pathways require the reaction of the carbon substrate with a nucleophile or a base in the rate-determining step of the reaction. So the presence of a good base or nucleophile favors these mechanisms over the S_N1 and E1 pair. Steric hindrance is an important factor in the competition between the S_N2 and E2 pathways. The fact that substitution is slowed by steric hindrance, whereas elimination is not, is reflected in the following examples. In these examples the presence of ethoxide ion, which is a strong base and a strong nucleophile, favors the S_N2/E2 mechanisms over the S_N1/E1 pathways. As the electrophilic carbon is changed from primary to secondary to tertiary, the mechanism changes from nearly complete S_N2 to complete E2 as the increasing steric hindrance at the electrophilic carbon slows the rate of the S_N2 reaction. Remember, E2 is not slowed by steric hindrance, so substrates with the leaving group on a tertiary carbon give E2 elimination rather than S_N1 substitution in the presence of a strong base.



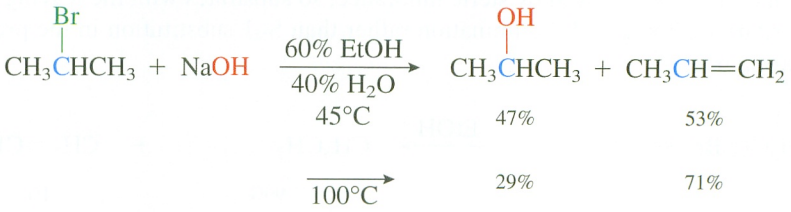
Chapter 8 discussed the observation that nucleophile strength increases as base strength increases (as long as the basic/nucleophilic atoms are from the same period of the periodic table). Therefore, the rates of both S_N2 and E2 reactions increase as the strength of the base and nucleophile increases. However, many experimental observations have shown that a stronger base (which is also a stronger nucleophile) tends to give a higher ratio of elimination to substitution than does a weaker base (which is also a weaker nucleophile). For example, the reaction of 2-bromopropane with ethoxide ion, a strong base and a strong nucleophile, results in 20% substitution and 80% elimination. In contrast, the reaction of 2-bromobutane with acetate

ion, a weaker base and a weaker nucleophile, results in a high yield of the substitution product.





The temperature of the reaction also affects the relative amounts of substitution and elimination. Usually, the percentage of elimination increases at higher temperatures. This results from the fact that elimination breaks the molecule into fragments and therefore is favored more by entropy than is substitution. As the temperature is increased, the entropy term in the equation $\Delta G = \Delta H - T\Delta S$ becomes more important and the amount of elimination increases. This effect is illustrated in the following equations:



In summary, in the competition between S_N2 and E2, nucleophiles that are weak bases, minimum steric hindrance, and lower temperatures are used to maximize substitution; strong bases, maximum steric hindrance, and higher temperatures are used to maximize elimination.

S_N1 and E1

Both of these mechanisms involve rate-determining formation of a carbocation, so they most commonly occur with tertiary (best) or secondary substrates in polar solvents. The reaction conditions are often neutral or acidic to avoid the presence of any strong base or strong nucleophile that might favor the S_N2 or E2 pathways. Because the step that controls which product is formed occurs after the rate-determining step, it is much more difficult to influence the ratio of substitution to elimination here. In general, some elimination always accompanies an S_N1 reaction and must be tolerated. An example is provided in the equation in Figure 9.7.

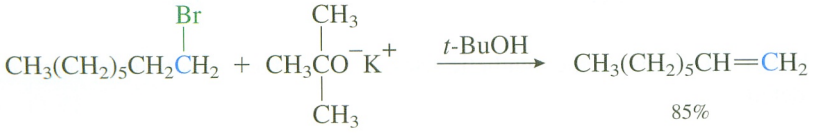
When substitution or elimination reactions are used in organic synthesis—that is, to prepare organic compounds—it is usually possible to control whether the substitution product or the elimination product is the major compound that is formed. From the viewpoint of the carbon substrate the use of these reactions in synthesis can be summarized in the following manner.

Methyl Substrates: CH_3L

Methyl substrates are excellent for S_N2 reactions. There is no β-carbon, so elimination cannot occur. Also, the methyl carbocation is very unstable, so the S_N1 mechanism does not occur either.

Primary Substrates: RCH_2L

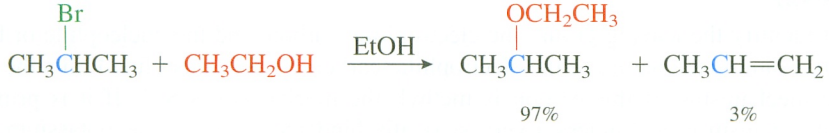
Because of their low amount of steric hindrance, these compounds are excellent for S_N2 reactions with almost any nucleophile. However, they can be forced to follow a predominantly E2 pathway by the use of a strong base that is not a very good nucleophile because of its steric bulk. Most commonly, potassium *tert*-butoxide is used in this role, as shown in the following equation:



Primary substrates do not follow the S_N1 or E1 mechanisms unless they are allylic or benzylic because primary carbocations are too high in energy.

Secondary Substrates: R_2CHL

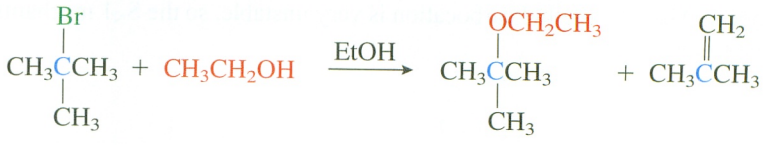
Secondary substrates can potentially react by any of the four mechanisms. They give good yields of substitution products by the S_N2 mechanism when treated with nucleophiles that are not too basic ($CH_3CO_2^-$, RCO_2^-, CN^-, RS^-, and others to be discussed in Chapter 10). They give predominantly elimination products by the E2 mechanism when treated with strong bases such as OH^- or OR^-. (Many examples were provided in the preceding discussion.) They give predominantly substitution by the S_N1 mechanism, accompanied by some elimination by the E1 mechanism, when reacted in a polar solvent in the absence of a good nucleophile or base (acidic or neutral conditions). As an example, the following equation illustrates the use of an alcohol as both nucleophile and solvent (called a **solvolysis reaction**) in the preparation of an ether by an S_N1 process. Note that the strongly basic EtO^- nucleophile cannot be used because it is a strong base and would cause elimination by the E2 mechanism to be the major process.



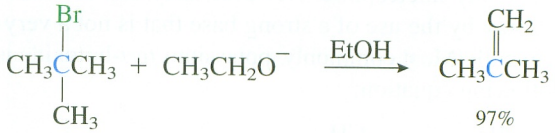
Tertiary Substrates: R_3CL

Tertiary substrates do not give S_N2 reactions because they are too hindered. Therefore, if a substitution reaction is desired, it must be done under S_N1 conditions (polar solvent, absence of base). Acceptable yields are usually obtained, but some elimination by the E1 pathway usually occurs also. Excellent yields of elimination product can be obtained

by the E2 mechanism if the substrate is treated with a strong base (usually OH^- or OR^-). Examples are provided in the following equations:



81% 19%



97%

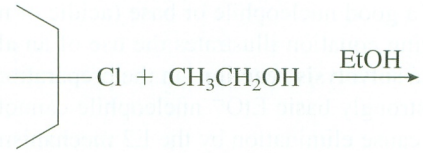
Chapter 10 discusses the synthetic uses of all of these reactions in considerably more detail.

PRACTICE PROBLEM 9.5

Show the substitution and/or elimination products for these reactions. Explain which mechanisms are occurring and which product you expect to be the major one.

a) $CH_3CH_2CH_2CH_2Cl + CH_3O^- \xrightarrow{CH_3OH}$

b) $CH_3CCH_2CH_3 + {}^-OH \xrightarrow{CH_3CH_2OH}$ (CH3 and Br on the carbon)

c) 

Strategy

First identify the leaving group, the electrophilic carbon, and the nucleophile or base. Then, examine the nature of the electrophilic carbon because this often limits the possible mechanisms. If this carbon is methyl, the mechanism is S_N2. If it is primary, the mechanism is S_N2 unless a very sterically hindered base, such as potassium *tert*-butoxide, is used to promote E2 elimination. If the electrophilic carbon is tertiary, the mechanism is S_N1 and E1 under acidic or neutral conditions (absence of strong base) and E2 in the presence of a strong base (usually HO^-, CH_3O^-, or $CH_3CH_2O^-$). If the electrophilic carbon is secondary, all of the mechanisms are available, so the nucleophile and the solvent must be considered. The presence of a good nucleophile that is only a moderately strong base ($CH_3CO_2^-$, RCO_2^-, CN^-, RS^-) suggests that the mechanism will be S_N2, especially if the solvent is aprotic. In the presence of a strong base (usually HO^-, CH_3O^-, or $CH_3CH_2O^-$), the mechanism will be E2. The mechanism will be S_N1 in the absence of good nucleophiles and strong bases (usually acidic or neutral

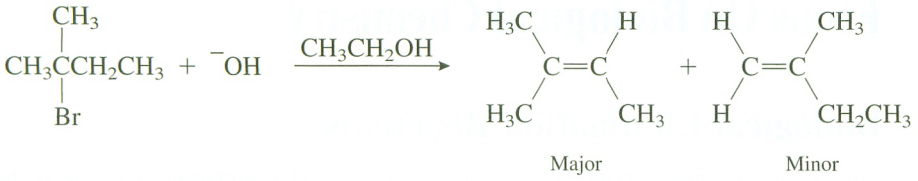
conditions) in a polar solvent. Do not forget about possible resonance stabilization of the carbocation, which makes an S_N1 reaction more favorable. Under favorable conditions (absence of good nucleophiles and strong bases), a compound that can form a resonance-stabilized carbocation can react by an S_N1 mechansim even when the electrophilic carbon is primary. Once you have decided on the mechanism that will be followed, consider the stereochemistry and regiochemistry of the reaction if they make a difference in the reaction (inversion for S_N2; racemization for S_N1; anti elimination and Zaitsev's rule for E2; and Zaitsev's rule for E1).

Solutions

a) The leaving group, Cl, is bonded to a primary carbon. Methoxide ion (CH_3O^-) is a strong nucleophile and a strong base but not sterically hindered, so the reaction will follow the S_N2 mechanism. Not much elimination should occur. There is no stereochemistry visible at the primary carbon.

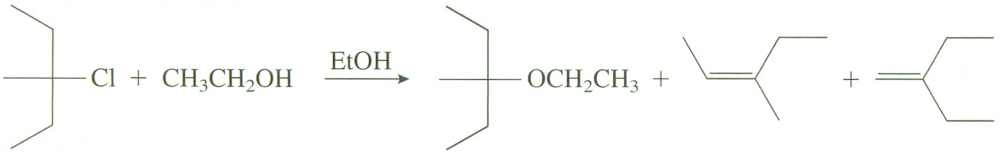
$$CH_3CH_2CH_2CH_2Cl + CH_3O^- \xrightarrow{CH_3OH} CH_3CH_2CH_2CH_2OCH_3$$

b) The leaving group (Br) is bonded to a tertiary carbon. Hydroxide ion is a strong base, so the E2 mechanism should be followed. According to Zaitsev's rule, the more highly substituted alkene should be the major product.



Major Minor

c) The leaving group is on a tertiary carbon and there is no strong base present, so the reaction follows the S_N1 and E1 mechanisms. Substitution is usually the major product, but a significant amount of elimination product is also formed. According to Zaitsev's rule, the more highly substituted product should predominate among the alkenes.



Major (S_N1) $Z + E$ Minor (E1) Trace (E1)

PROBLEM 9.15

Show the substitution and/or elimination products for these reactions. Explain which mechanisms are occurring and which product you expect to be the major one.

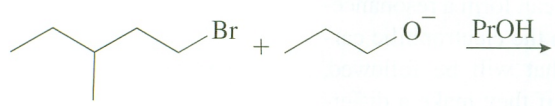
a) $CH_3CH_2\underset{\displaystyle OTs}{\underset{|}{C}}HCH_3 + CH_3CH_2\overset{\displaystyle O}{\overset{\|}{C}}O^- \xrightarrow{CH_3CH_2CO_2H}$

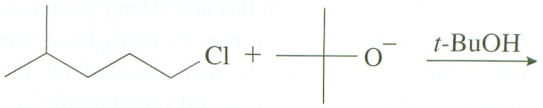
b) $CH_3CH_2\underset{\displaystyle OTs}{\underset{|}{C}}HCH_3 + CH_3CH_2O^- \xrightarrow{EtOH}$

c) $PhC(CH_3)_2Cl + CH_3OH \xrightarrow{CH_3OH}$

PROBLEM 9.16

Explain which mechanism is preferred in these reactions and show the major products:

a) 

b) 

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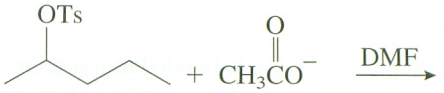
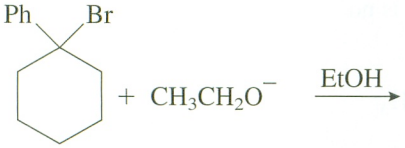
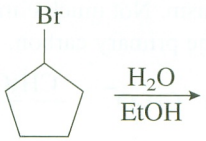
d) 

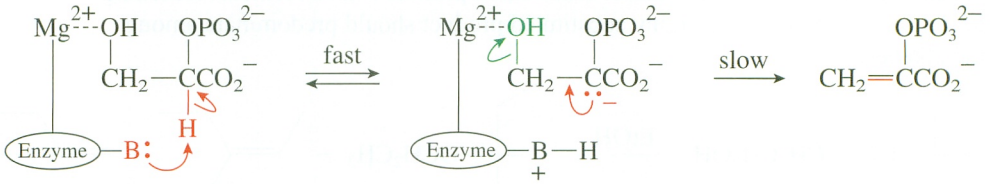
e) 

f) 

Focus On Biological Chemistry

Biological Elimination Reactions

Elimination reactions occur in living organisms also. One important example is the conversion of 2-phosphoglycerate to phosphoenolpyruvate during the metabolism of glucose:



2-Phosphoglycerate Phosphoenolpyruvate

This elimination is catalyzed by the enzyme enolase and follows an E1cb mechanism. The enzyme supplies a base to remove the acidic proton and generate a carbanion in the first step. In addition, a Mg^{2+} cation in the enzyme acts as a Lewis acid and bonds to the hydroxy group, making it a better leaving group.

Another example occurs in the citric acid cycle, where the enzyme aconitase catalyzes the elimination of water from citrate to produce aconitate:

Citrate Aconitate

Review of Mastery Goals

After completing this chapter, you should be able to:

- Provide a detailed description, including stereochemistry, for the E2 mechanism and summarize the conditions that favor its occurrence. (Problems 9.20, 9.21, 9.23, and 9.24)
- Provide similar information about the E1 mechanism. (Problems 9.19, 9.28, and 9.33)
- Understand Zaitsev's rule and Hofmann's rule and when each applies. (Problem 9.17)
- Show the expected products, including stereochemistry and regiochemistry, of any elimination reaction. (Problems 9.17, 9.22, 9.27, 9.34, 9.36, and 9.37)
- Predict whether the major pathway that will be followed under a particular set of reaction conditions will be S_N1, S_N2, E1, or E2. (Problems 9.18, 9.25, and 9.26)

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Visual Summary of Key Reactions

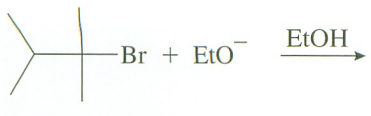
The two mechanisms for the elimination reactions that compete with substitutions are summarized in Table 9.1.

Table 9.1 Summary of Elimination Mechanisms

	E1	E2
Mechanism	Two steps R—L ⟶ R^+ ⟶ alkene	One step R—L + B^- ⟶ alkene + BH + L^-
Kinetics	First order rate = k[RL]	Second order rate = k[RL][B^-]
Competes with	S_N1	S_N2
Stereochemistry	No preferred conformation	Anti-periplanar elimination (*trans*-diaxial in cyclohexanes)
Regiochemistry	Zaitsev's rule: favors more highly substituted alkene	Zaitev's rule: favors more highly substituted alkene (Hofman elimination follows Hofman's rule: favors less highly substituted alkene)
	Conjugated always preferred	Conjugated always preferred
Competition with Substitution	Some E1 always accompanies S_N1	E2 favored by strong bases, steric hindrance, and higher temperatures

Additional Problems

9.17 Show the elimination products of these reactions. When more than one product is possible, indicate which product is major.

a) 

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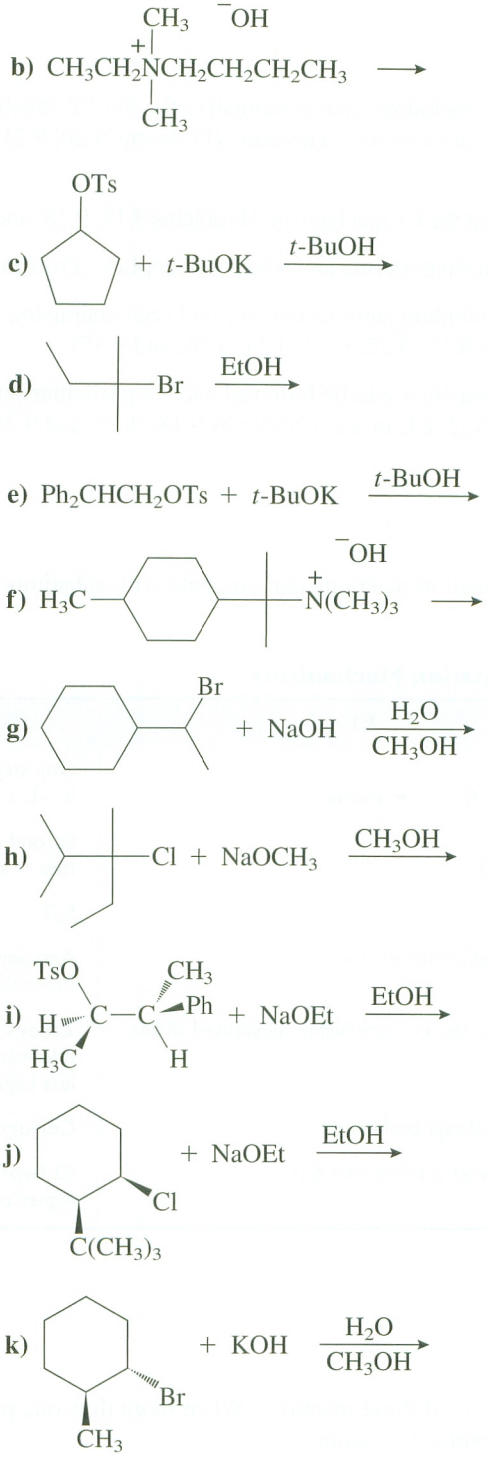
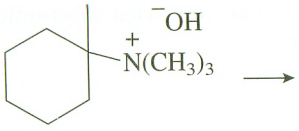
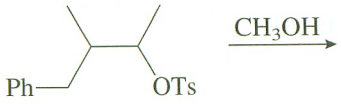
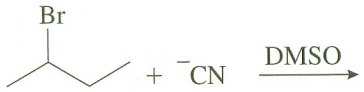
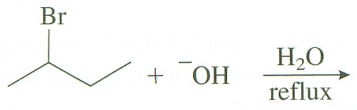

b) CH3CH2N+(CH3)(CH3)CH2CH2CH3 OH− →
c) OTs + t-BuOK t-BuOH →
d) Br EtOH →
e) Ph2CHCH2OTs + t-BuOK t-BuOH →
f) H3C N+(CH3)3 OH− →
g) Br + NaOH H2O / CH3OH →
h) Cl + NaOCH3 CH3OH →
i) TsO H C C CH3 Ph H H3C + NaOEt EtOH →
j) Cl C(CH3)3 + NaOEt EtOH →
k) Br CH3 + KOH H2O / CH3OH →

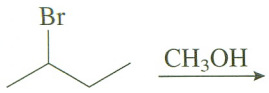
l) 

m) 

9.18 Explain which reaction mechanism (E1, S_N1, E2, S_N2) these reactions follow, and show the major products:

a) 

b) 

c) 

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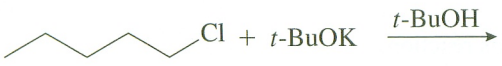
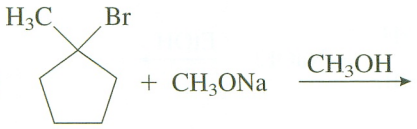
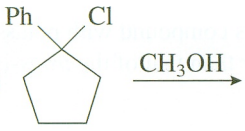
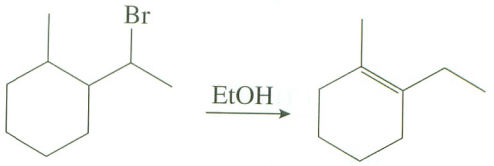
e) 

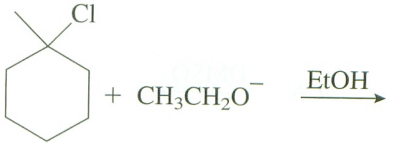
f) 

g) 

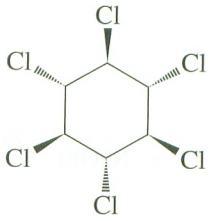
9.19 Show all the steps in the mechanism for this reaction. What substitution product(s) would also be formed in this reaction?



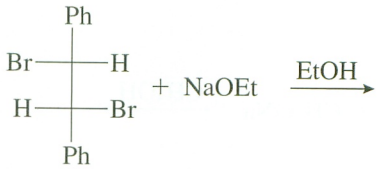
9.20 Show the products of this reaction. How would the composition of the products change if *t*-BuO^- in *t*-BuOH were used in place of ethoxide ion in ethanol?



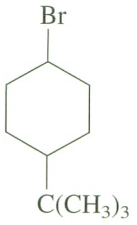
9.21 All of the stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane have very similar rates of E2 reaction except the following stereoisomer, which reacts about 7000 times more slowly than the others. Explain.



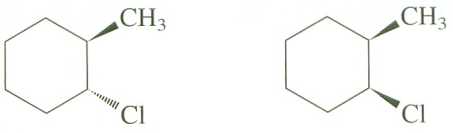
9.22 Show the product of this reaction:



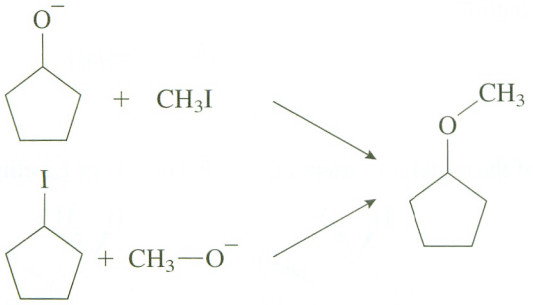
9.23 Explain why the reaction of the *cis*-isomer of this compound with potassium *tert*-butoxide in *tert*-butanol is about 500 times faster than that of the *trans*-isomer.



9.24 Explain which of these compounds has a faster rate of E2 elimination:



9.25 Frequently, several different routes can potentially be used to synthesize a desired compound. For example, the following two routes can be envisioned for the preparation of cyclopentyl methyl ether. Explain which of these two routes you expect to give the higher yield of the desired ether.



9.26 What reagents and reaction conditions could be used to carry out the following transformations?

a) $CH_3CH_2CH_2CH_2\underset{\displaystyle Br}{\underset{|}{C}}H_2 \longrightarrow CH_3CH_2CH_2CH{=}CH_2$

b) $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}Cl \longrightarrow CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}OCH_3$

c) $PhCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}Cl \longrightarrow \underset{\displaystyle H}{\overset{\displaystyle Ph}{\overset{|}{\underset{|}{C}}}}{=}\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}$

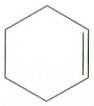
d) $CH_3CH_2\underset{\displaystyle OTs}{\underset{|}{C}}HCH_2CH_3 \longrightarrow CH_3CH{=}CHCH_2CH_3$

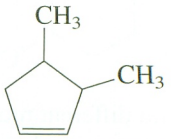
e)

f)

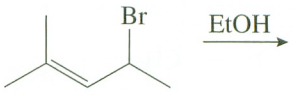
9.27 Suggest the best way to prepare these alkenes from alkyl halides.

a) $CH_3CH_2CH_2CH_2CH{=}CH_2$ **b)** $CH_3CH_2CH_2CH{=}CHCH_2CH_3$

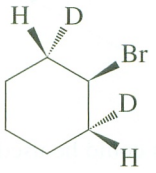
c) 

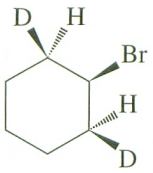
d) 

9.28 When heated in ethanol, this alkyl halide gives two substitution and two elimination products. Show the structures of these products and the mechanism for their formation.

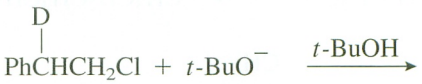


9.29 Which of these stereoisomers has the faster rate of E2 elimination?

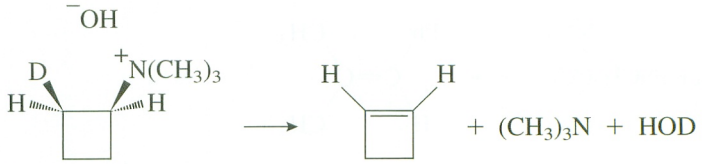




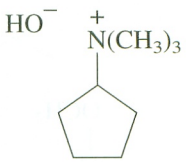
9.30 Show the products of this elimination reaction and explain which is major:



9.31 Explain why deuterium is lost in preference to hydrogen in this Hofmann elimination reaction:



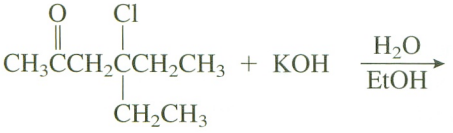
9.32 Explain why this compound gives about 50% syn elimination when heated:



9.33 When 2-bromo-2-methylbutane is heated in a mixture of ethanol and water, it gives a 64% yield of substitution products and a 36% yield of elimination products.

a) What mechanisms does this reaction follow?
b) Show the structures of the substitution products.
c) Show the structures of the elimination products.
d) Under the same reaction conditions, how would 2-iodo-2-methylbutane differ from the bromide in its rate of reaction? in the products of its reaction?

9.34 This elimination reaction gives a single product. Show its structure and explain why it is the only product formed.



9.35 How might the structure of DDT be modified to make it again effective against resistant insects?

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9.36 Explain which product is formed when each of these alkyl bromides reacts with sodium ethoxide in ethanol.

9.37 Explain which of these alkyl chlorides reacts faster with sodium ethoxide in ethanol.

9.38 Explain which product is formed when each of these alkyl chlorides reacts with sodium ethoxide in ethanol.

9.39 Explain which elimination product is formed when this alkyl chloride is heated in ethanol.

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